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PRE-APPEAL BRIEF REQUEST FOR REVIEW	Docket Number (Optional) 223002107200	
	Application Number 10/814,480	Filed March 29, 2004
	First Named Inventor Nicholas M. VALIANTE, Jr	
	1617	Examiner Y.S. Chong

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal. A final rejection was mailed 24 June 2008, a Notice of Appeal is therefore due 24 September 2008.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant /inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [x] attorney or agent of record. Registration number 44.422
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34.

/Michael G. Smith/
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September 24, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[x] *Total of 1 forms are submitted.

sd-442856

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Pre-Appeal Brief Request for Review

The claims at issue encompass a vaccine composition that provides an enhanced immune response to an antigen by combining the antigen with a "benzazole compound adjuvant" of Formula XXI. The claims require that the "*benzazole adjuvant is present in an amount effective to enhance the immune response in a subject to the antigen...*" Though Formula XXI encompasses compounds that were known in the prior art (Chamberlain, et al., US Patent Application 2005/0234083), their effect of enhancing an immune response was not known before the present invention. This effect is an aspect of the claimed invention that makes it both valuable and nonobvious.

The sole outstanding rejection is one for obviousness. The obviousness rejection of each claim relies upon a combination of two cited references, and the Applicants believe the rejection is improper. Applicants request this review for the following reasons:

Reason 1: the rejection does not view the prior art from the perspective of one of ordinary skill.

The Examiner based a rejection of all claims on obviousness, alleging that it would have been obvious to combine compounds of Formula XXI as disclosed in Chamberlain with a particular vaccine composition disclosed in Klaviniskis, US Patent Application 2003/014792, because both were said to be useful to treat cancer. Klaviniskis discloses vaccine compositions containing a bacterium spore (*B. subtilis*) that acts as an adjuvant to enhance an immune response, combined with an antigen. Various antigens can be used, and at least some of such compositions are said to be useful to treat certain cancers. Because both the compounds and the vaccine compositions were generally referred to in the prior art as useful for treating cancer, the Examiner alleged it would have been obvious to use the two compositions together. Relying upon *In re Kerkhoven*, a case holding that it was *prima facie* obvious to combine two detergents together into a single detergent composition, the Examiner concluded that it was obvious to combine compounds of Formula XXI with the Klaviniskis vaccine compositions, to arrive at a composition within the scope of the claims. In doing so, however, the Examiner ignored any and all considerations that a person of ordinary skill in the art (PHOSITA) would consider before

mixing together two different types of pharmaceutical compositions that operate by very different mechanisms.

This is a dramatically different situation from *In re Kerkhoven*, where two detergents were mixed together to form another detergent. The materials in *Kerkhoven* were being used "for the very same purpose", while the Chamberlain compound and the Klaviniskis vaccine treat cancers by quite different mechanisms—one affects cancer cells directly while the other affects the subject's immune system—and thus should not be considered to perform 'the very same purpose'. The fact that both can be used to 'treat cancer' is not really analogous to the mixing of detergents in *Kerkhoven* and should not justify blind reliance upon that case as a basis to conclude the claims are obvious. Moreover, use together does not require mixing these two together, and there is no evidence that they would have been used to treat cancer by the same route of administration, or on a similar dosing schedule, or that they could be mixed together without affecting each other. Chamberlain says its compounds can be administered in many different ways, and that they can be used with other cancer treatments; however, it does not disclose or suggest MIXING its compounds with vaccines.

The proper determination of obviousness must be made from the perspective of a person of ordinary skill in view of the references and the person's general skills and knowledge. Failure to consider what the person of ordinary skill would have thought about when deciding whether to mix two pharmaceutical compositions together is inconsistent with a proper obviousness analysis. This is not a system where the person of ordinary skill routinely mixes together compositions with no regard to dosing profiles, potential interactions, etc., and should not be decided by analogy to a case like *In re Kerkhoven*, which involved a far simpler system. The identity of the PHOSITA, and the level of skill in the art, were not established during prosecution. However, a pharmaceutical manufacturer, for example, would not casually mix a drug with a vaccine into a single composition without thinking about whether they are used at similar frequencies, administered by the same routes, or are likely to interact with each other, etc.: there is simply no *need* to do so, and too many differences in the way such items are used to justify doing so. They can be separately used to treat a single patient without being mixed; indeed, *mixing them produces a product that would be less useful*, because the mixture would limit the ability to administer each composition according to its optimal characteristics. The

person of ordinary skill might expect the adjuvant in a vaccine composition to cause immune reactions to a drug added to the composition, since that is the purpose of an adjuvant, and the drug is likely to be administered repeatedly, while the vaccine is not. Using two treatments together does not require mixing them together; and in view of the expected differences in administration, they ordinarily would *not* be mixed by a person of ordinary skill. The Examiner has alleged that mixing drugs with vaccines is known, but has provided no evidence to support that assertion, which goes well beyond the type of statement that can fairly be accepted as 'generally known'. Ignoring the things a PHOSITA (pharmaceutical manufacturer, for example) would think about before mixing pharmaceutical compositions having different effects is NOT a proper obviousness analysis, when the sole reason to mix them is they both can be used to treat cancer. Applicants believe that the person of ordinary skill would know that vaccines are commonly delivered by injection, while small molecule therapeutics are more typically taken orally which would weigh against combining Chamberlain and Klaviniskis; and that small molecule therapeutics are not normally combined with vaccines for reasons such as those discussed herein. *Kerkhoven* is insufficient to render the combination of these materials *prima facie* obvious.

In addition, the Examiner imposed this obviousness rejection without even establishing the level of skill in the art, or identifying the person having ordinary skill in the art (PHOSITA). It is virtually impossible to make a correct obviousness determination without identifying the level of skill in the art. It is one a key part of the analysis for obviousness outlined in *Graham v. John Deere*. Blind reliance upon a fact pattern like *Kerkhoven*, which is dramatically different, does not comport with a proper obviousness determination, which should ask what the person of ordinary skill would have thought about before combining the teachings of the cited the references. Failure to even consider the subject matter from the perspective of the person of ordinary skill contradicts *Graham v John Deere*, which is Supreme Court authority.

Reason 2: The rejection improperly disregards an express claim limitation.

The claims require an amount of a compound of formula XXI that is effective to enhance an immune response. The Examiner relied upon the fact that the reference discloses a range of amounts of a compound of Formula XXI that *could* be used for the treatment in the reference, arguing that the range 'must' overlap with or include the 'effective amount' of the claims. This

again fails to consider what a person having ordinary skill in the art would have done in view of the references. Based on Chamberlain, the PHOSITA would have determined an effective amount of a compound of Formula XXI for a cancer treatment. The amount that would have been selected *might* be sufficient to enhance an immune response, but if so, that would be entirely by chance, and that amount would NOT be the whole range of possible amounts from Chamberlain. Equally importantly, this is really an inherency rejection layered over an obviousness rejection, and is contrary to the case law for relying upon inherency. Even if one mixed the two compositions together, one would not have included *all possible amounts of a compound of Formula XXI that fall within the range mentioned in the reference*. Effective amounts for the purpose of the present claims may well overlap with the range in Chamberlain, but that is not enough to support an inherency-based rejection under clear Federal Circuit precedent: the claimed invention cannot be found obvious unless the result of combining the prior art would necessarily include an amount of the compound meeting the claim limitation. MPEP 2112(IV): "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)." The fact that in some cases a *treatment* amount of the compound of Formula XXI might be an appropriate amount to meet the claim limitation is plainly insufficient to establish obviousness. Based on the references, even if the PHOSITA were to mix a cancer treatment composition of Chamberlain with a cancer vaccine composition from Klaviniskis, the PHOSITA would not necessarily have selected an amount of a compound of Formula XXI meeting the limitation of the claims, because the amount would have been selected to provide a therapeutic effect, not to provide an immune-enhancing effect. Thus obviousness has not been established, because combining the compositions in view of what the references teach would not necessarily have included the effective amount of the compound of Formula XXI that is required by the claims.

Reason 3: the claimed invention provides an unexpected advantage that overcomes any allegation of obviousness.

The Examiner also improperly ignored evidence of an effect that is entirely unexpected in view of the prior art. The invention provides a method of enhancing an immune response by using a compound according to the claims; this was acknowledged to be enabled. Nevertheless,

the Examiner fails to recognize that the enabled effect of the claimed composition is EVIDENCE on the record of an unexpected advantage. The prior art does not provide any reason to expect the compositions of the claim to provide such an effect: this effect could NOT have been foreseen from prior art. This unexpected effect is the core of the claimed invention, which demonstrates that the invention as a whole was nonobvious. Even if a *prima facie* case for obviousness were established, this unexpected effect achieved by the claimed invention overcomes any allegation of obviousness.

In view of the above, the invention as claimed is not rendered *prima facie* obvious by the cited references, because a person of ordinary skill would not have combined the compounds of Formula XXI with the vaccines of Klaviniskis to form a single composition. In addition, if the compounds of Chamberlain were combined with the vaccines of Klaviniskis, the combination would have been based on the reference teachings and would not necessarily or inherently have included an effective amount of the compound of Formula XXI. Thus the combination does not meet all limitations of the claims, so it cannot support an obviousness rejection. Finally, even if a *prima facie* case for an obviousness rejection were presented, it is overcome by the unexpected immune response-enhancing effect of the claimed compositions. The obviousness rejection is overcome and should be withdrawn.

Dated: September 24, 2008

Respectfully submitted,

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